Global Response to the H1N1 Pandemic

Deployment of vaccine in developing countries

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World Health Organization

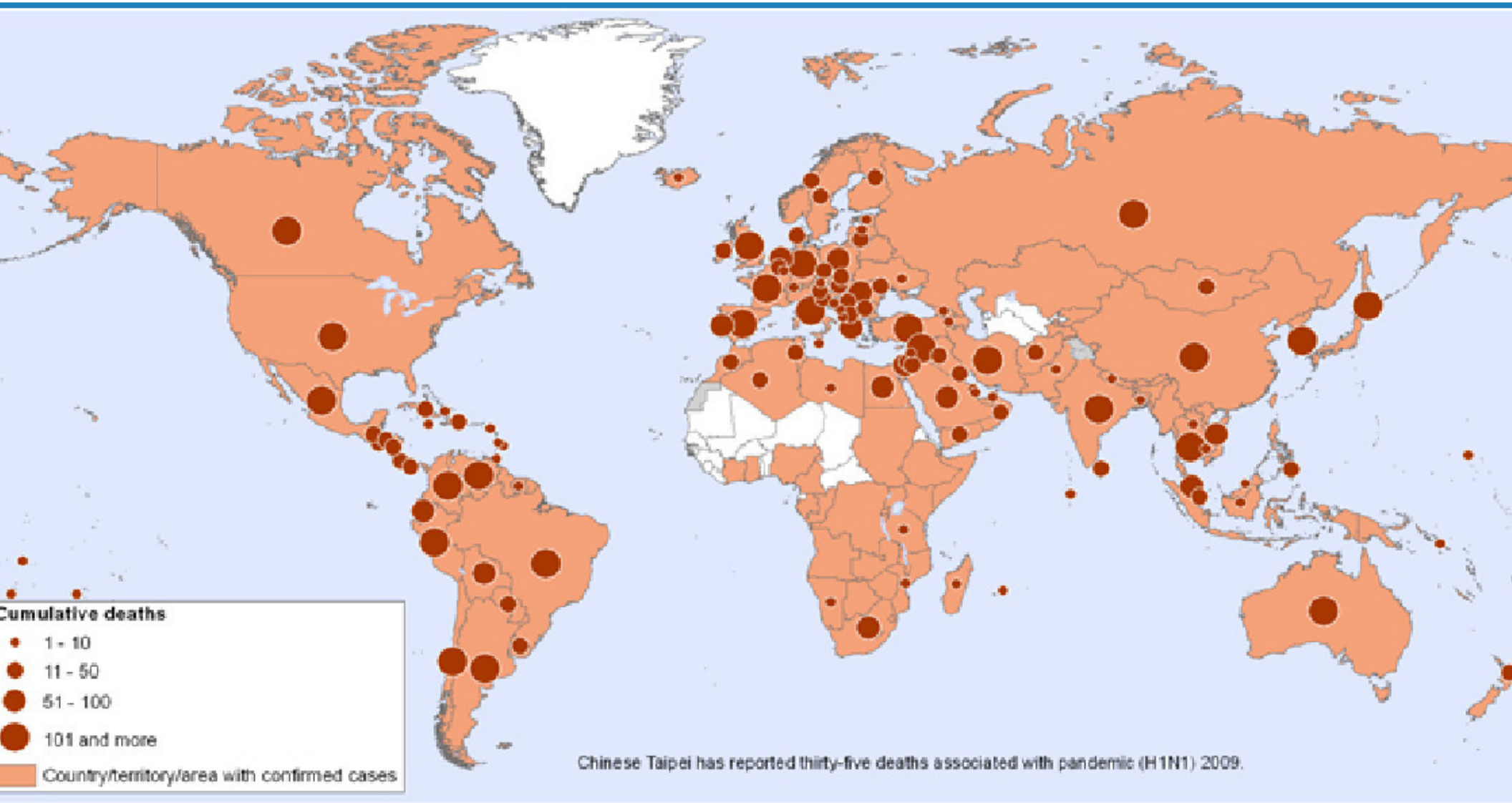
Outline

1. Update on pandemic characteristics and public health response
2. Pandemic (H1N1) vaccine deployment

Pandemic Overview
(January 2010)

- As of 3 January 2010, worldwide more than 208 countries and overseas territories or communities have reported laboratory confirmed cases of pandemic influenza H1N1 2009, including at least 12799 deaths.
- As many countries have stopped counting individual cases, particularly of milder illness, the case count is significantly lower than the actually number of cases that have occurred.
- The most active areas of pandemic influenza transmission currently are in parts of central, eastern and southeastern Europe, North Africa, and South Asia.

Global Spread of Pandemic (H1N1) 2009
as of January 3, 2010



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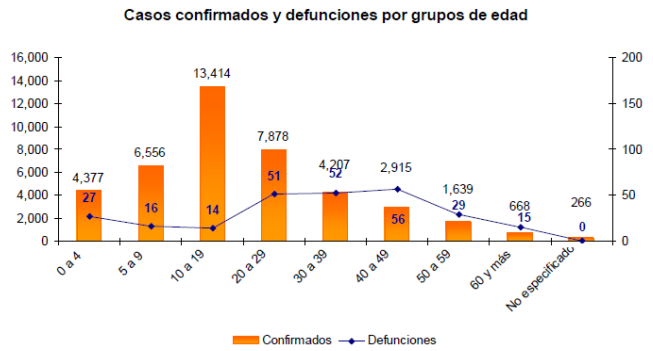
Age group affected

- Age groups between 5 to 49 mostly affected
- Age group distribution of the disease seems to follow the age pyramid in each country
- Difference of median age between mild, severe and fatal cases.
- Comparison between countries is difficult due to (i) the different age classes used to present the data and (ii) the use of crude number of cases rather than rates.

Distribution of confirmed cases by age group (number of cases)

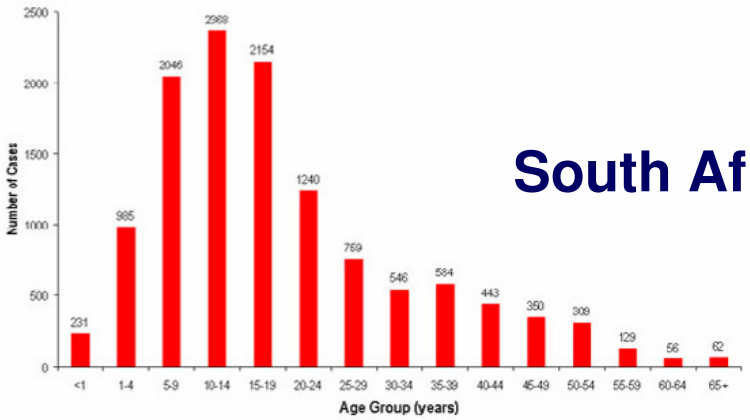
Casos confirmados y defunciones por grupos de edad

(41,920 casos confirmados y 260 defunciones)



FUENTE: Casos confirmados: Base de datos InDRE; Defunciones: CONAMED.

Mexico



South Africa

Figure 2: Number of laboratory confirmed pandemic influenza A(H1N1) 2009 cases by age-group, South Africa, updated 19 October 2009 (n=12 378, 116 unknown age)

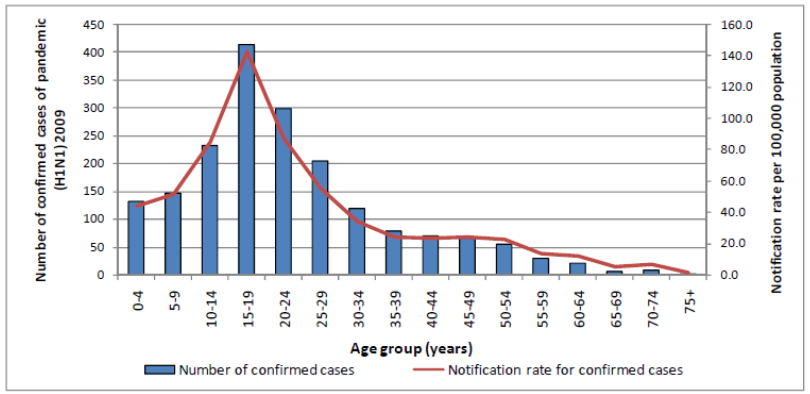
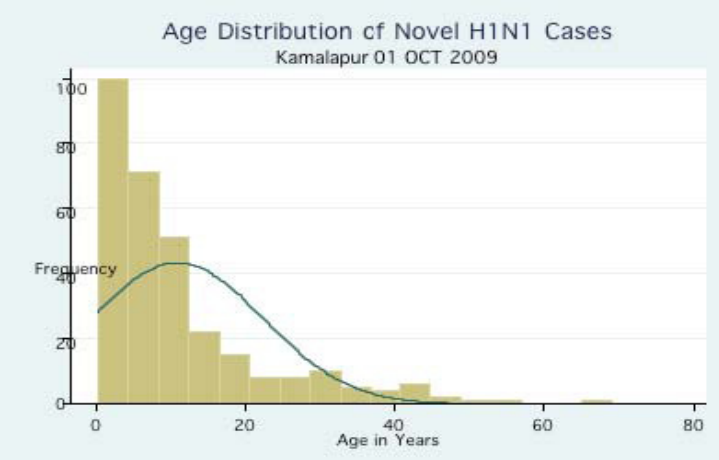


Figure 8: Cumulative number of confirmed cases of pandemic (H1N1) 2009 and notification rate per 100,000 population by age group (years)

Source: CIDR

Ireland



Bangladesh

Age-Specific (population based) hospitalization rates (Australia, Chile, Argentina, New Zealand)

FIGURE 8

Rates of notified and hospitalised influenza A(H1N1)v cases by age group, New Zealand, cumulative rates for 2009

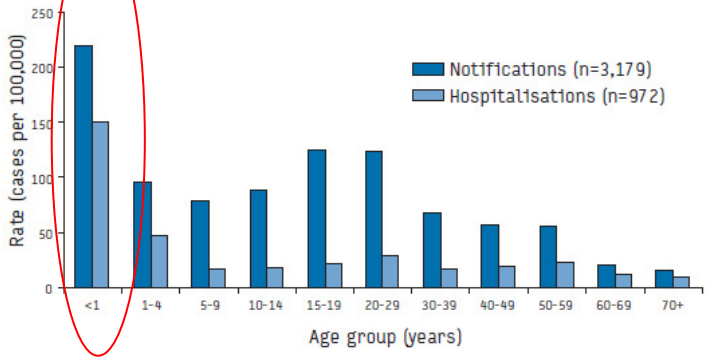


Gráfico 2: Distribución de IRAG según grupos de edad. Tasas por cien mil hab. Argentina 2009. n= 8.872

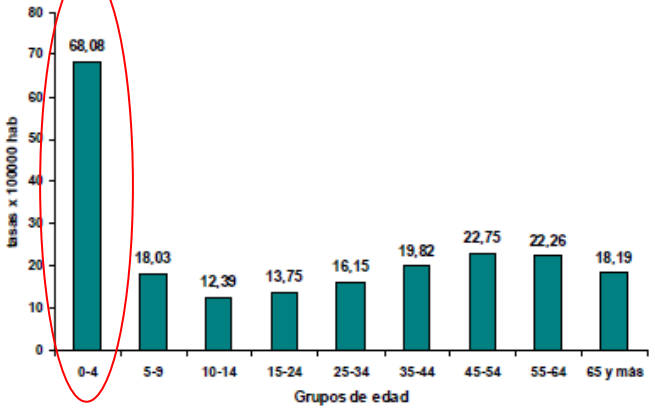
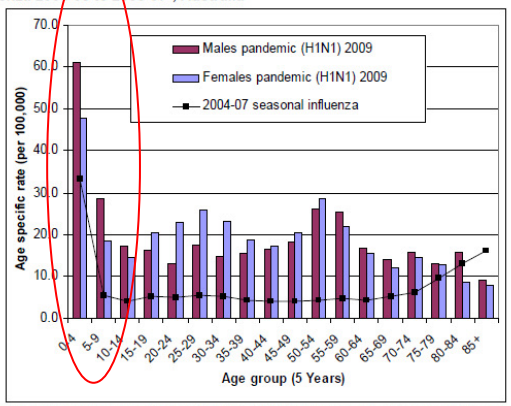


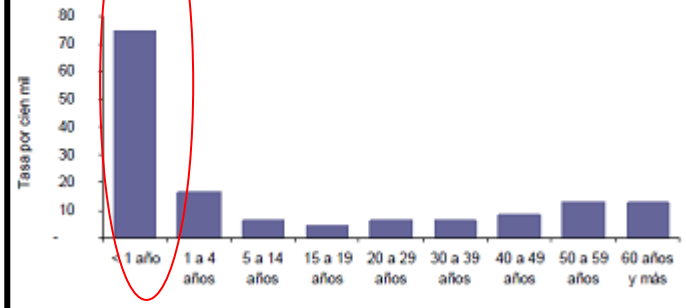
Figure 9. Age specific rates of hospitalised confirmed cases of pandemic (H1N1) 2009 to 18 September 2009, compared with average annual age specific rates of hospitalisations from seasonal influenza 2004-05 to 2006-07*, Australia



*The rates for pandemic (H1N1) 2009 are from 15 June to 21 August 2009 whereas the rates for seasonal influenza are averaged annual rates (i.e. for a full influenza season).

Source: NETEPI database

Gráfico 5: Distribución de las tasa de IRAG confirmadas de influenza pandémica (H1N1) 2009, según grupos de edad. Chile, 2009. n= 1562



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ledian age is shifting to older age with severit

- **Laboratory-confirmed** cases: median age 12-28 yrs
- **Hospitalized** cases: median 20-36 yrs
- **ICU admissions:** median 36-46 yrs
- **Fatal** cases: median 35-51 yrs

Pregnancy and Influenza: Outcomes in Pregnant Women

- 10 times higher ICU hospitalization comparing to general population
- 7-10% of hospitalized (including ICU) being pregnant women

Neuzil et al. Amer J Epidmiol 148:1094, 1998; Dodds et al. Can Med Assoc J 176:463, 2007; Rasmussen et al. Emerg Infect Dis 14:95, 2008; ANZIC NEJM 361, 2009, JAMA Oct 2009

Pandemic (H1N1) 09 virus characteristics

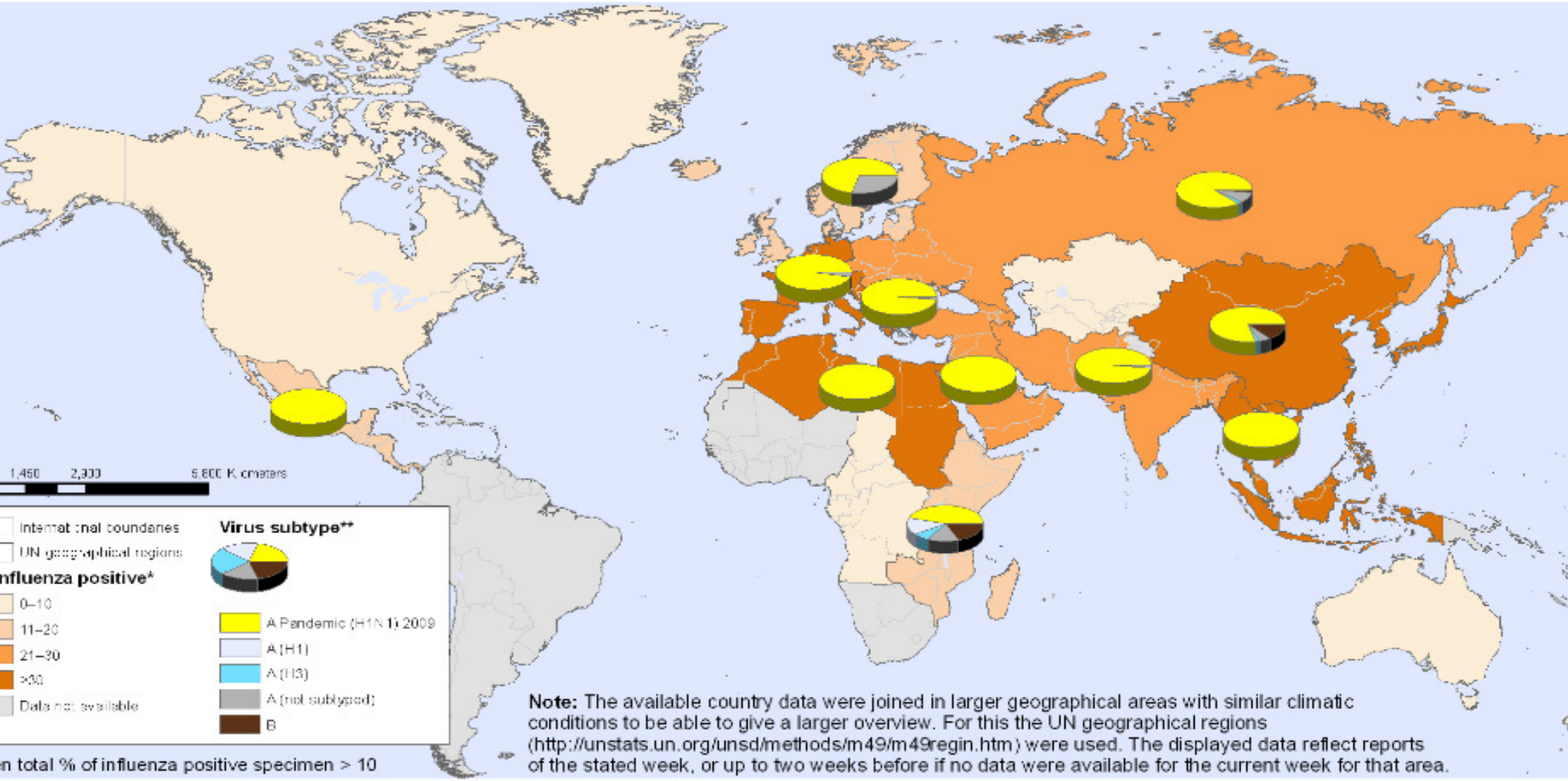
- All viruses analyzed to date are
  - **Antigenically, similar to A/California/7/2009, WHO recommended pandemic vaccine virus**
  - Genetically, homogenous to the vaccine virus A/California/7/2009 with minor variations
  - Viruses isolated from severe cases do not show sequence differences
- **Sensitive to neuraminidase inhibitors** (oseltamivir, zanamivir)
  - Resistant to amantadine and rimantadine
  - **Sporadic resistant virus to oseltamivir reported:** During the week December 25 - December 31, 16 new cases of oseltamivir-resistant pandemic (H1N1) 2009 influenza viruses have been reported bringing the cumulative total to 184
  - All resistant viruses showed H275Y mutation
  - An animal study showed same pathogenicity in mice of oseltamivir resistant or sensitive pandemic 2009 viruses
- Virus evolution (genetically and antigenically) is unpredictable

Pandemic (H1N1) 2009 and seasonal influenza viruses co-circulation, and H5N1

- Pandemic (H1N1) 2009 and seasonal viruses have co-circulated at varying levels over time in multiple countries –
- Pandemic (H1N1) 2009 (as % of detections) in:
  - Chile: ~90%; USA: > 98% (since mid-June)
  - Victoria, Australia: ~67%; South Africa: 41% (sentinel surveillance, till Oct)
- Patterns in upcoming northern hemisphere season are uncertain
  - H3N2 quickly disappearing when H1N1 transmission reaches significant levels e.g. China

rcentage of specimen tested positive for influenza

Status as of week 5
20–26 December 200



Data Source: World Health Organization
Map Production: Public Health Information and Geographic Information Systems (GIS)
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Historical & Contemporary Concerns Broadly Shaped Influenza Pandemic Preparedness

- Severity and disruption of 1918 pandemic
- Political and programmatic consequences of 1976 Swine flu vaccination
- Renewed focus on (re)-emerging infectious diseases
- Rapid extensive multisectoral impact of 2003 SARS
- Global spread, lethality and persistence of H5N1 viruses
- Increasing convergence of health and non-health issues within intergovernmental discussions

Such Broad Concerns Supported Significant Actions

- Initiation of WHO's global influenza surveillance late 1940's–early 1950's
- Intensified national preparedness planning (including by U.S.) after emergence of avian H5N1 in 1997
- Passage of International Health Regulations in 2005
- Launching of WHO Global Action to increase supply of pandemic vaccine in 2006
  - Linked pandemics with seasonal vaccine use & expanded manufacturing capacity
- WHO preparedness guidelines in 1999, 2005, 2009

Before H1N1 Pandemic, Many Questions Related to Pandemic Vaccines

- How much vaccine would be available in time give:
  - Limited global manufacturing capacity and production surge capacity
  - Potentially limited yields and immunogenicity based on H5N1 vaccines
  - Estimated 5 months from virus identification to first supplies becoming available for use
- Who would assume liability?
- How would recipient target groups be identified & enforced?
- How would vaccine be delivered, administered & kept secure?
- Would unresolved virus & benefits sharing issues slow the process?
- Would countries hold or nationalize manufacturing capacities or supplies?

When H1N1 Pandemic Started, WHO Initiated a Broad Set of Actions

Overall Objective

Mitigate the impact of pandemic influenza on people and countries

- Monitor and Track the Disease Progression
- Generate and Transfer Knowledge
- Guide and Support Countries
- **Accelerate Access to Vaccines**
- Accelerate Access to Antivirals
- Global Health Leadership and Collaboration

Within Vaccine Area, Four Particular Priorities

- Facilitate rapid development and manufacture of pandemic vaccine
- Provide guidance on use of pandemic vaccine
- Monitor vaccine safety
- Open or increase vaccine access for developing & middle income countries

Objectives of WHO Vaccines Deployment Initiative

- Ensure access to vaccines for LICS/LMICS in need
- WHO Director General and UN Secretary General called for international solidarity to meet donation target of 10% population coverage for countries in need
- Several donor governments and 5 manufacturers have pledged support
- WHO is directing and coordinating the deployment of donations and provision of technical/operational support in collaboration with UNSIC, donors and others

SAGE July 7 recommendation for the use o pandemic vaccine

- Front-line HCWs (1-2% of population) to protect the health care system.
- Specific groups to reduce morbidity and mortality :
  - pregnant women,
  - individuals aged of >6 months with one of several chronic medical conditions
  - Healthy young adults (aged >15 years and <49 years)
  - Healthy children.
  - Healthy adults aged >49 years and <65 years
  - Healthy adults aged >65 years

WER, 24 JULY 2009, No. 30, 2009, 84, 301–308, http://www.who.int/wer

Eligibility and Sequencing (1)

Basket of principles for defining the sequence of distribution of WHO H1N1 pandemic influenza vaccine (not in any ranking order) :

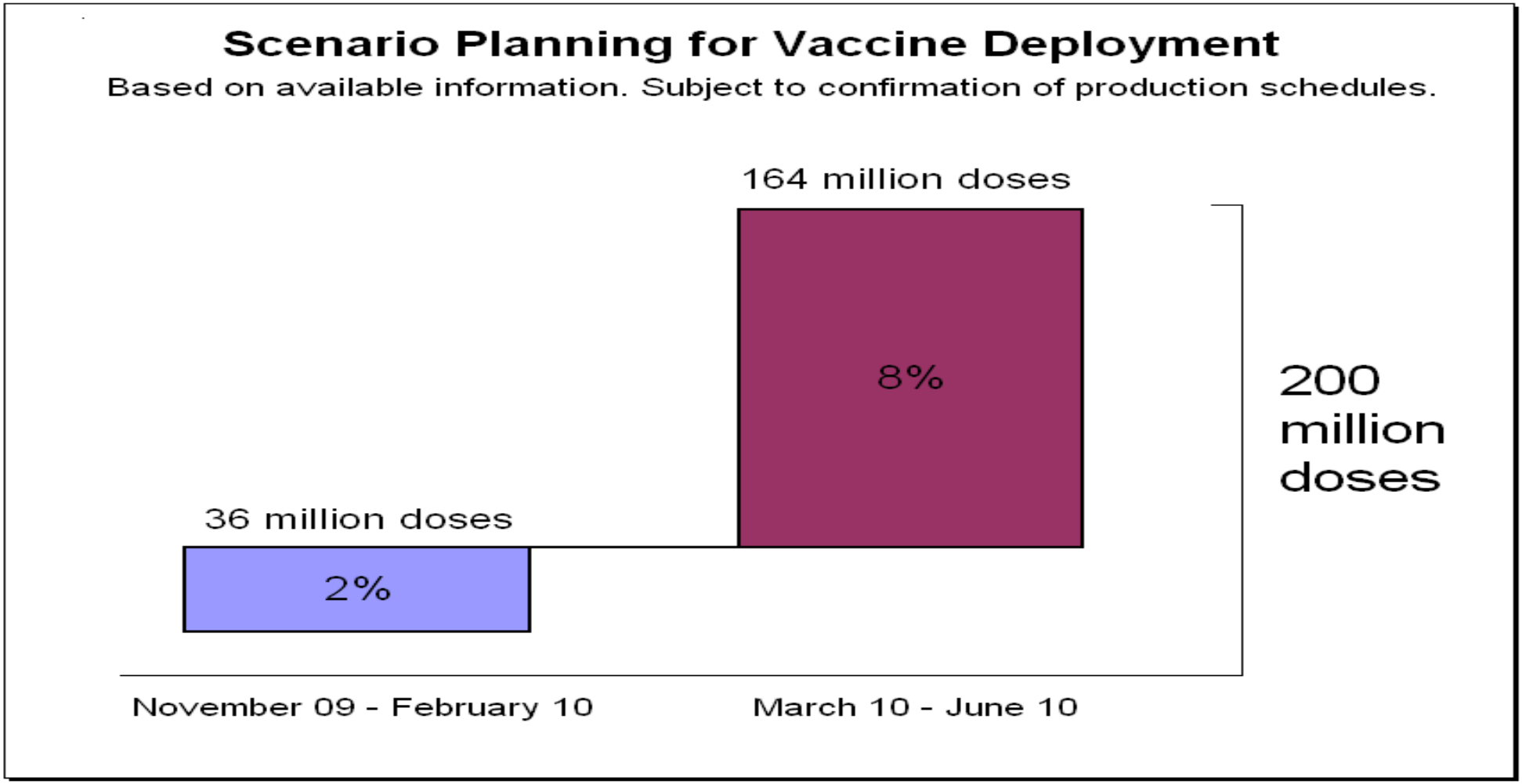
1. Vulnerability considerations

- Geography:
in the first 6 months (starting November): 2/3 of supplies to the Northern hemisphere, 1/3 to SH, because number of cases in the decline currently in the SH, and rising in the North; after April 2010, 2/3 SH, 1/3 NH.
- Disease burden:
in the same hemisphere, countries with highest ratio of death/inhabitant will be served first.

2. Readiness considerations

- Programmatic aspects:
i.e. readiness to vaccinate (plan, logistics, priority groups identified etc).
- Contractual arrangements:
fulfilment of legal requirements (Letter of Intent, signature of Agreement with WHO including agreement to waiver of or fast-track registration, assumption of liability)

Eligibility & Sequencing (2)



Regional allocation of donated vaccine

Region	Eligible countries	Millions to vaccinate
Africa	44	75.02
Americas	10	7.59
Europe	8	11.55
Eastern Mediterranean	7	26.29
South-east Asia	9	55.66
Western Pacific	17	23.76
Totals	**95**	**199.87**

95 Countries eligible for WHO pandemic vaccine support

Afghanistan	Comoros	Ghana	Maldives	Timor-Leste	Papua New Guinea
Angola	Congo	Guatemala	Philippines	Mali	Paraguay
Armenia	Cook Islands	Guinea	Republic of Moldova	Mauritania	Togo
Azerbaijan	Côte d'Ivoire	Guinea-Bissau	Rwanda	Mauritius	Tokelau
Bangladesh	Cuba	Guyana	Samoa	Mongolia	Tonga
Benin	Democratic People's Republic of Korea	Haiti	Sao Tome and Principe	Mozambique	Tuvalu
Bhutan	Democratic Republic of the Congo	Honduras	Senegal	Myanmar	Uganda
Bolivia	Djibouti	Indonesia	Seychelles	Namibia	Ukraine
Botswana	El Salvador	Kenya	Sierra Leone	Nauru	United Republic of Tanzania
Burkina Faso	Equatorial Guinea	Kiribati	Solomon Islands	Nepal	Uzbekistan
Burundi	Eritrea	Kyrgyzstan	Somalia	Nicaragua	Vanuatu
Cambodia	Ethiopia	Lao People's Democratic Republic	Sri Lanka	Niger	Viet Nam
Cameroon	Fiji	Lesotho	Sudan	Nigeria	Yemen
Cape Verde	Gabon	Liberia	Suriname	Niue	Zambia
Central African Republic	Gambia	Madagascar	Swaziland	Occupied Palestinian Territories	Zimbabwe
Chad	Georgia	Malawi	Tajikistan	Pakistan	

Terms of Support

- Before a country can receive vaccines some key requirements must be met, including:
  - Letter of Intent sent to WHO
  - Signature of formal Agreement with WHO including acceptance of liability for any rare adverse events/side effects
  - Submission of a completed, vetted in-country deployment plan
- Countries must also agree to:
  - Ensure registration of the vaccine or otherwise authorize its use in the country
  - Commit to appropriate and ethical use of the vaccine donation
  - Agree to handle the importation, customs clearance and distribution of the vaccine
  - Agree to notify WHO of the occurrence of any unexpected adverse events, or an unexpected high occurrence of adverse events

Update on Donations

- 13 donor governments*
- 5 donor manufacturers**
- 190 M vaccine doses pledged
- 74.5 M syringes pledged
- US$ 46M pledged for operations

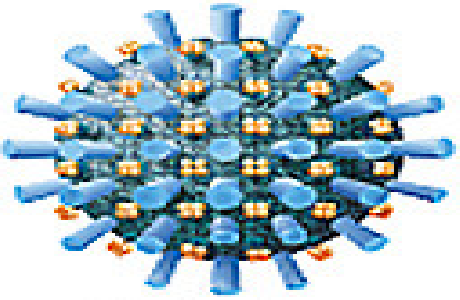
Overview of resource mobilization (millions)				
Resource	**Need**	**Pledge**	**Committed**	**Gap**
Vaccines (doses)	200	189.84	83.1	10.16
Syringes	200	74.5	45	125.5
Safety boxes	2	0.5	0.5	1.5
US$ for global operations	62.6	45.94	20.44	16.66
US$ for in-country operations	170	33.08	5.38	136.92

*Australia, Belgium, Brazil, Canada, France, Germany, Italy, Japan, New Zealand, Singapore, Switzerland, Thailand, UK, USA (and the Bill and Melinda Gates Foundation)

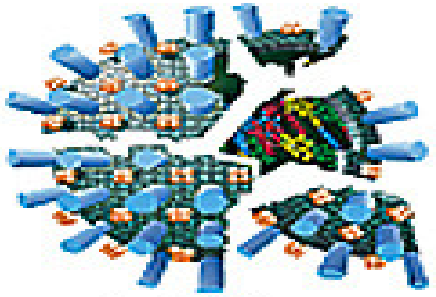
**Becton-Dickinson, CSL, GSK, MedImmune, Sanofi Pasteur, Temptime

Types of licensed monovalent pandemic influenza A (H1N1) 2009 vaccines

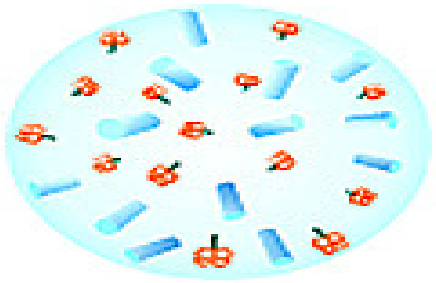
(Source: IFPMA-IVS)



Whole virus



Split virus



Subunit
(surface antigen)

Live attenuated

Baxter (EMEA) **Ommnivest (Hungary)**	**8 manufacturers, (China)** ***CSL (Australia; US)** ***Sanofi Pasteur (US)** **Green Cross (Korea)** ***GSK ASO3 (EMEA, Canada)**	***Novartis (US)** ***Novartis+M59 adjuvant (EMEA)**	***MedImmune (US)** **Microgen (Russia)**

*** Donated to WHO**

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Public concerns about the safety of pandemic H1N1 influenza vaccines

- **Guillain–Barré syndrome**

  (GACVS 2009)
  - the underlying reasons for the association observed in 1976 are unknown

  - since then, either no association with GBS or, in a few studies, a very small risk (app. 1 case/1.000.000 vaccinations)

  - importance of preparing for active surveillance for GBS syndrome and availability of background rates

- **Adjuvanted influenza vaccines** *(GACVS 2009)*
  - relatively small scale experience, especially in risk groups

  - potential for higher reactogenicity

  - autoimmune events following immunization

- **Squalene** *(GACVS 2006)*
  - fears of squalene in vaccine inducing pathological anti-squalene antibodies are unfounded

  - but experience of squalene-containing vaccines has been primarily in older age-groups
  http://www.who.int/wer/2006/wer8128.pdf

- **Thiomersal** *(GACVS 2008)*
  - no evidence of toxicity in infants, children or adults exposed to thiomersal in vaccines

- **Risks in special groups (eg. pregnancy)**
  -Risk-benefit of influenza vaccination during pregnancy, at all stages,

  - given the high risk to the mother - and thus to the fetus - of the disease itself, and (as far as is known) the small potential risk to mother and fetus of the seasonal inactivated influenza vaccine, SAGE made recommendations in July 2009.

Safety of pandemic H1N1 vaccines in clinical trials

- Most of the evidence generated on phase 2 trials with H1N1 vaccines, and by reference to H5N1 pandemic vaccines
- Profile – most reactions mild in nature, of short duration, fewer reaction with second dose (inactivated vaccines=blue, LAIV=orange)

Very common	**Administration site conditions (induration, swelling, pain, redness), fever, chills, fatigue, headache, arthralgia, myalgia**	**Rhinorrhoea, nasal congestion, irritability, malaise**	**Cough, lethargy, headache, sore throat, myalgia**
Common		**Sweating**	**Fever, chills, abdominal pain**
		Lymphadenopathy, dizziness, influenza like illness, cough, rhinorrhoea, nasal congestion, malaise	
Uncommon			**Pruritus, rash, urticaria, diarrhoea, vomiting, abdominal pain, nausea, insomnia, paraesthesia**

Safety monitoring of pandemic H1N1 vaccines in large-scale usage

- Safety information becoming available from Australia, Canada, China, Denmark, France, Hungary, Ireland, Japan, Korea, Netherlands, Norway, Sweden, Switzerland, USA,

Started in September
Australia, China, Hungary, Oman

Started in October
Austria, Belgium, Canada, Finland, France, Germany, Japan, Mexico, Norway, Portugal, Republic of Korea Sweden United Kingdom USA

Started in November
Bahrain, Cyprus, Denmark, Ireland, Israel, Jordan, Kuwait, Netherlands, Qatar, Romania, Russia, Saudi Arabia, Singapore, Spain, Switzerland, Turkey, UAE

Countries starting campaigns in January 2010:
Azerbaijan, Afghanistan Iran, Mongolia

Safety of pandemic H1N1 vaccines in large-scale usage

- More than a 200 million doses of H1N1 vaccines have been administered to HCW, people in high risk groups and the general population since September 2009.
- Relatively low number of local and systemic reactions reported so far
- Number of severe events small, mainly allergic reactions
- Small number of deaths reported around the time of vaccination; so far follow-up indicates unrelated causes
- Quick validation and follow-up of severe cases essential.
- GACVS concluded on 5 December 2009 that no unexpected safety concerns have been identified for any of the H1N1 vaccines used in population-level immunization programmes thus far

SAGE October 28 recommendation on pandemic vaccines

- Number of doses :
  - Public health considerations support the use of a **single dose of vaccine** in **adults, adolescents from 10 years of age and above**, provided this use is consistent with regulatory authorities' indications.
  - In the context of limited vaccine supplies, priority should be given to provide **one dose of vaccine** to as many children as possible where priority has been assigned to this group by national authorities. A second dose can provided as further supplies become available. if recommended by regulatory authorities.
- Safety in pregnant women : in the absence of a specific contra-indication by the regulatory authority, any licensed pandemic vaccine can be used to protect pregnant women.
- Co-administration : when seasonal and pandemic vaccines are both inactivated, or when one is inactivated and the other is live attenuated, that they can be co-administered

Pandemic vaccine prequalification status 8 January 2010

Manufacturer	H1N1 Vaccine	Brand name	Production country	Status
GlaxoSmithKline Biologicals, S.A.	Adjuvanted	**Arepanrix ®**	Canada	Prequalified
	Adjuvanted	**Pandemrix ®**	Germany	Prequalified
Sanofi Pasteur S.A.	Non-adjuvanted	**Panenza ®**	France	Pending
	Non-adjuvanted	**n/a**	United States of America	Pending
Novartis AG	Non-adjuvanted	**Fluvirin ® H1N1**	United Kingdom	Prequalified
	Adjuvanted	**Focetria ®**	Italy	Prequalified
	Adjuvanted	**Celtura ®**	Germany	Prequalified
CSL Limited	Non-adjuvanted	**Panvax ®**	Australia	Prequalified
MedImmune	Live-attenuated	**n/a**	United States of America	Pending

Current situation (January 8, 2010, 95 countries) - 1

- 86 of the 95 countries have requested vaccine donations.
- 28 countries have signed agreements with WHO.

Progress of national deployment plans	
Stage of preparation	**Number of countries / % of 95**
Compete and final	9 (9.5%)
Being finalized - expected in Q1 2010	24 (25.2%)
Early development - expected in 2010	62 (65.3%)

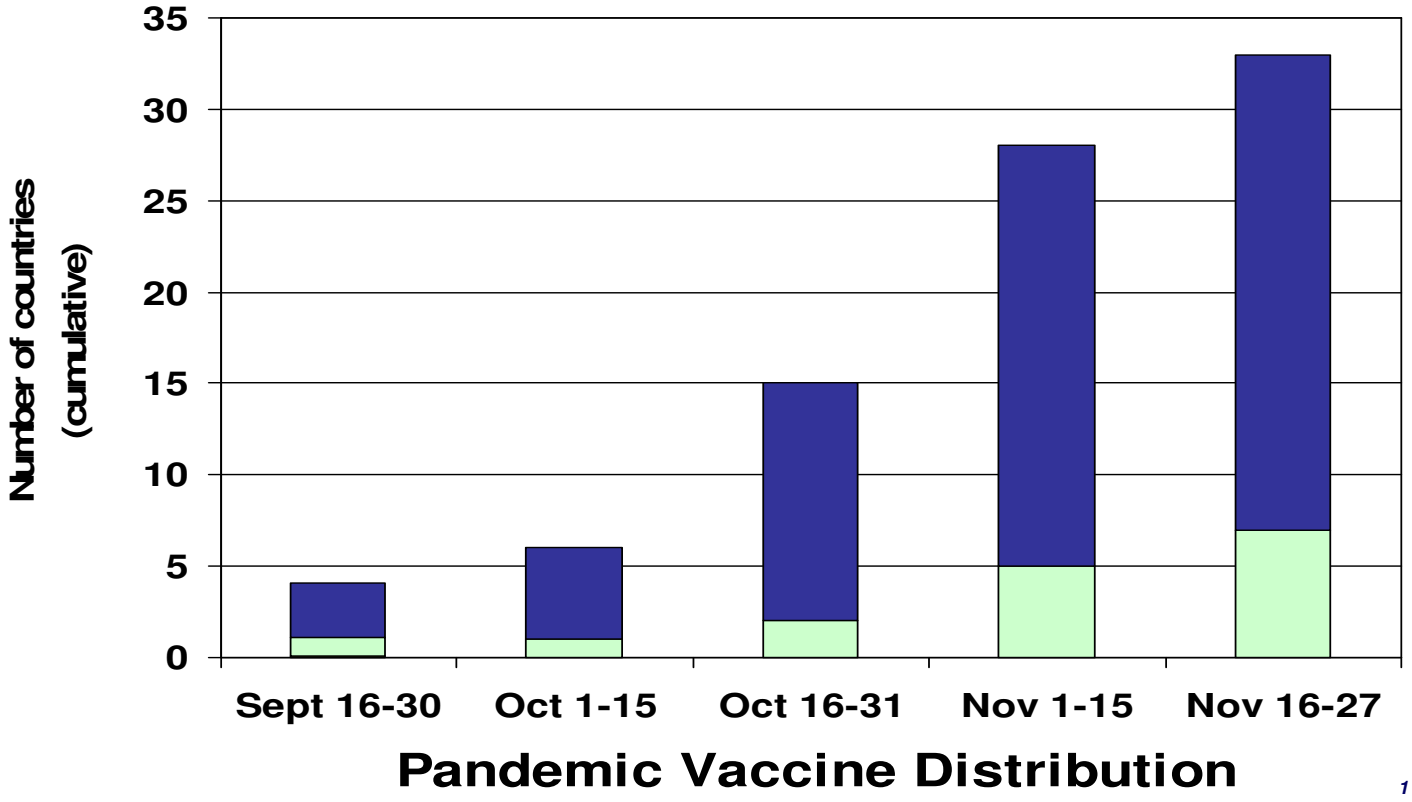
Current situation - 2

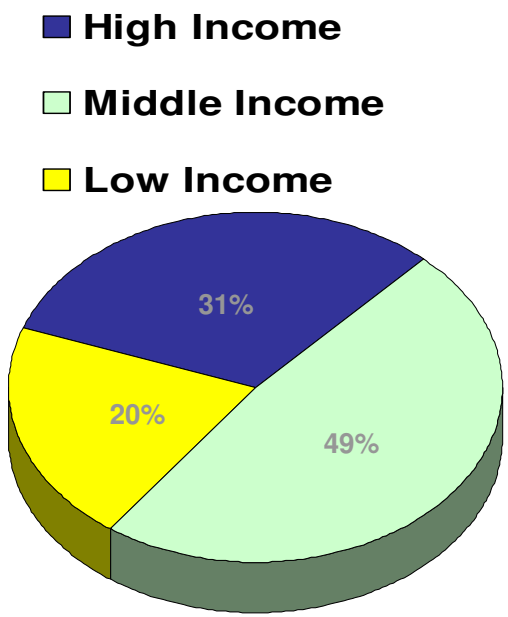
- WHO with partners has delivered vaccines and/or ancillary products to 5 countries and is preparing to supply several others.

Deliveries		
Country	**Products**	**Date of arrival in country**
Afghanistan	Safety boxes	19 December 2009
Azerbaijan	Vaccines, safety boxes and syringes	08 January 2010
Mongolia	Vaccines, safety boxes and syringes	07 January 2010
Sri Lanka	Safety boxes	26 December 2009
Ukraine	Safety boxes	24 December 2009

Vaccine Deployment has been slower then expected

- Initial available vaccines mostly to developed countries
- Vaccine roll out to low income countries slower than hoped
- First donated doses arrived in Azerbaijan & Mongolia in January 2010





World economies[1]

[1] *World Bank classification 2009*

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What are the Complexities?

- Very tight time frames imposed by rapid spread of pandemic and changing expectations of population
- Ad hoc negotiations because there is no over-arching framework
- Difficult for manufacturers to match demand
  - On an absolute scale
  - On an as needed basis (i.e., similar to cash flow)
- Balancing retention of vaccines for domestic use and donations to support to global solidarity

More Complexities…

- Extreme logistical & legal issues
  - Need for standard approaches but multiple vaccines and countries
  - Need for new approaches such as liability agreements by recipient countries
- Communications
  - Intense mis-information campaigns by some anti-vaccine groups
- Insufficient funding

Concluding remarks

- Preparedness was essential and significantly improved this response overall compared with the past
  - But it was incomplete with many gaps
- Flexibility was and remains essential
  - No degree of planning fully anticipates reality
- Complexities of improving access to vaccines demonstrates the limitations of an ad hoc approach
  - A framework for future pandemics will be an essential component of better preparedness